FluMist®
Influenza Virus Vaccine Live, Intranasal
Safety Monitoring
in Children Aged <5 Years

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
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General Approaches to Safety Monitoring for New Vaccines or Vaccines with New Indications

- Review pre-licensure safety data
- Identification of potential risks from phase 3 pre-licensure trials
- Review of available postmarketing data
- Vaccine Adverse Event Reporting System (VAERS) monitoring plan
- Vaccine Safety Datalink (VSD) project plan: assessment of risk through near real-time or planned studies
- Identification/creation of
  - Key case definitions
  - Candidate protocols
  - Need for special studies

Pre-licensure Primary Safety Study MICP11: Methods

- Multi-center, randomized (49% US)
  - Study group: FluMist®* + IM placebo (saline) (N=4243)
  - Active control group: trivalent inactivated influenza vaccine (TIV) + intranasal placebo (saline) (N=4232)
  - Subjects excluded if history of severe asthma or medically diagnosed or treated wheezing within 42 days before enrollment
- Two pre-specified safety wheezing outcomes from dose 1 through 42 days after the last vaccine dose
  - Primary: Medically significant wheeze
  - Secondary: Any wheeze

*Influenza Virus Vaccine, Trivalent types A and B, Live Cold Adapted, liquid formulation (2004-2005 influenza strains)

Sources: FDA and MedImmune briefing documents, FDA VRPBAC meeting, May 16, 2007; Belshe NEJM 2007.

Pre-licensure Primary Study MICP11: Primary Wheezing Safety Finding: Medically Significant Wheeze (MSW) FluMist® vs. TIV

- Age 6-23 months: Increased risk for MSW after FluMist®
- Age 24-59 months: No increased risk for MSW after FluMist®

Age Mo.	FluMist® N (%)*	TIV N (%)*	Relative Risk (95% CI)
6-23	117 (5.9%)	75 (3.8%)	1.55 (1.17, 2.05)
6-11†	47 (6.9%)	29 (4.2%)	1.62 (1.04, 2.53)
12-23†	70 (5.4%)	46 (3.6%)	1.50 (1.05, 2.16)
24-59	46 (2.1%)	56 (2.5%)	0.83 (0.56, 1.21)

*Number in FluMist®=4179; TIV=4173.

†Not a pre-specified age group for analysis

Sources: FDA and MedImmune briefing documents, FDA VRPBAC meeting, May 16, 2007; Belshe NEJM 2007.

Pre-licensure Primary Study MICP11: Reactogenicity and Serious Adverse Events

- Compared with TIV recipients, FluMist® recipients aged 6-59 months had
  - More frequent reports of runny nose/ nasal congestion and low-grade fever after 1st dose
  - Similar serious adverse event (SAE) rates through 180 days (3.3 % FluMist® vs. 3.1% TIV)
- In a post-hoc analysis, Flumist® recipients aged 6-11 months had increased risk for all-cause hospitalization through 180 days:
  - FluMist® (6.1%) vs. TIV (2.6%)

Sources: FDA and MedImmune briefing material, FDA VRPBAC meeting, May 16, 2007; Belshe NEJM 2007.

Adverse Events after FluMist® Reported to VAERS 8/1/2003–2/28/2007

Age Group	All Reports	Serious Reports (%)*
6-23 months*	1	0
2-4 years*	14	0
5-17 years	266	14 (5.2%)
18-49 years	370	27 (7.3%)
≥50 years*	26	1 (3.8)
Unknown	67	1 (1.5%)
Total	744‡	43 (5.8%)

* Percentage of total reports in corresponding age-group

† Outside the licensed age group

‡ Crude reporting rate 10.9 total reports per 100,000 doses distributed

Source: Hua W, Haber P, Izurieta H, unpublished VAERS data

VAERS FluMist® Reports: Selected Respiratory Conditions 8/1/2003–2/28/2007

Age	All reports	Reported main condition (%)*		
		Asthma/ wheezing	Pneumonia	Bronchitis
6-23 mo	1	0	0	0
2-4 yrs	14	0	0	0
5-17 yrs	266	16 (6%)	7 (3 %)	2 (1 %)
≥18 yrs	396	5 (13%)	6 (2%)	4 (1%)
Unknown	67	1 (2%)	2 (3%)	2 (3%)
Total	744	22 (3%)	15 (2%)	8 (1%)

* Percentage of total reports in corresponding age-group

Source: Hua W, Haber P, Izurieta H, unpublished VAERS data

VAERS FluMist® Reports of Asthma/Wheeze by Medical History 8/1/2003–2/28/2007

Age	All	Asthma/Wheezing Adverse Event Report			
		Total*	Asthma History/ Wheeze	Other chronic condition history	No history
6-23 mo	1	0	0	0	0
2-4 years	14	0	0	0	0
5-17 years	266	16 (6%	7	0	9
≥18 years	396	5 (13%)	3	0	2
Unknown	67	1 (2%)	0	0	1
Total	744	22 (3%)	10	0	12

* Percentage of total reports in corresponding age-group

Source: Hua W, Haber P, Izurieta H, unpublished VAERS data

Key Safety Questions about FluMist® Use in Young Children

- Will screening for a history of wheezing identify children appropriately?
- Is the safety profile of FluMist® within 6 weeks after vaccination comparable to TIV in children aged <5 years?
  - Is the risk for medically-attended wheeze increased?
  - Is the risk for all-cause hospitalization increased?
  - Are there other unexpected safety signals?
- Are children with a history of wheezing at increased risk for wheeze or hospitalization after FluMist®, compared with those with no history?

VAERS Post-Marketing Surveillance for FluMist® Vaccine

- National passive surveillance system for reporting vaccine adverse events
- Limitations
  - Risk of underreporting or reporting bias
  - Possibly incomplete, unreliable data
- CDC / FDA scientists will review daily alerts of serious adverse event (SAE) reports* and other medically important conditions, including wheezing after FluMist®

*Code of Federal Regulations 21CFR600.80 Serious adverse event defined as involving hospitalization or prolongation of hospitalization, death, life-threatening illness or permanent disability

Vaccine Safety Datalink Project (VSD)

- Collaboration between CDC and 8 mangaged care organizations MCOs with comprehensive medical and immunization histories of 5.5 million people per year
- Limitations
  - Limited power to assess risk for rare adverse events
  - Inability to monitor vaccine safety in near real-time if vaccine uptake is limited in MCOs

Vaccine Safety Datalink (VSD) and FluMist®

- To date, limited use of FluMist® in VSD sites, except as part of ongoing Phase 4 study*
- VSD will examine rates of clinically important outcomes in children aged <5 years, including
  - Medically-attended wheezing
  - All-cause hospitalization
- FDA licensure and ACIP recommendation decisions and uptake in VSD sites will affect specific aims and methods of VSD study/studies

*CDC has no involvement with this study; sources: MedImmune briefing document, FDA VRPBAC meeting, May 16, 2007 and Product Approval Information 2003, available at http://www.fda.gov/cber/approvltr/inflmed061703L.htm

Additional FluMist® Safety Activities

- The Brighton Collaboration to develop standardized case definitions for wheezing/asthma outcomes
- Education and outreach to providers and parents
  - Vaccine Information Statement
- MedImmune phase 4 study*
  - Population of 60,000 FluMist® recipients aged 5-49 years within the Kaiser Permanente system
  - Results anticipated 2011

*CDC has no involvement with this study; sources: MedImmune briefing document, FDA VRPBAC meeting, May 16, 2007 and Product Approval Information 2003, available at http://www.fda.gov/cber/approvltr/inflmed061703L.htm

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Background Slides

FluMist® Product History

- **June 2003**: FluMist (frozen) licensed for use in healthy persons aged 5-49 years (should not be administered to individuals without a history of asthma or reactive airway disease)

- **January 2007**: FluMist liquid formulation licensed to replace frozen formulation (first widespread use anticipated during 2007/08 influenza season)

- **May/June 2007:** FDA Vaccine and Related Product Biologics Advisory Committee (VRPBAC) reviewed MedImmune's Biologics License Application supplement for use of FluMist (liquid) in children aged aged 12-59 months without a history of wheeze/asthma; currently under FDA review

FDA Vaccines and Related Product Advisory Committee Meeting, May 16, 2007

Questions 2: Do the data demonstrate that the benefits will exceed the risk of FluMist® for use in

A. The applicant's proposed population (children 12 to 59 months of age without a history of wheeze/asthma)
   - Vote –Yes: 9 and No: 6

B. Children in the age strata 6-23, regardless of wheezing history?
   - Vote –Yes: 3 and No: 12

C. Children in the age strata 24-59 months, regardless of wheezing history?
   - Vote –Yes: 15 and No: 0

Source VRPBAC transcript, page 256, available at http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4292t1.pdf

Pre-licensure Primary Study MICP11: Wheezing Outcomes*

- Primary: Medically Significant Wheeze (MSW): Wheezing on physical exam and ≥1
  - Sign of respiratory distress (tachypnea, retractions, or dyspnea)
  - Hypoxemia (O2 sat <95%), or
  - New prescription for daily bronchodilator therapy (not on an "as needed" basis)
- Secondary: "Any wheezing" reported by clinician or parent
  - MedDRA preferred terms: wheeze, asthma, bronchospasm, bronchilolitis

*Occurring from receipt of dose 1 through 42 days after the last dose

Sources: FDA and MedImmune briefing documents, FDA VRPBAC meeting, May 16, 2007; Belshe NEJM 2007.

Use of Wheezing History and Outcomes in FluMist® Study MICP11

- Exclusion Criteria: Severe asthma, wheeze within 42 days
- Criteria for stratification: recurrent wheeze history
- Post-hoc analysis to assess association between history of wheeze and certain adverse events
- Pre-specified safety outcomes
  - Primary: Medically significant wheeze (MSW)
  - Secondary: Any wheezing

Source: MedImmune briefing document, FDA VRPBAC meeting, May 16, 2007

Selected Adverse Events after FluMist® Reported to VAERS: 8/1/2003–7/31/2005

Main Condition	All Reports (%)*	Serious Reports (%)*
Respiratory	217 (47.2%)	15 (37.5%)
Asthma	12	5
Pneumonia	10	5
Constitutional	67 (14.6%)	4 (10%)
Allergic	54 (11.7%)	6 (15%)
Abdominal	33 (7.2%)	1 (2.5%)
Ear-nose-throat	18 (3.9%)	0
Neurological	10 (2.3%)	7 (17.5%)
GBS*	3	3
Bell's Palsy	1	1
Cardiovascular	10 (2.2%)	3 (7.5%)
Ocular	7 (1.5%)	1 (2.5%)
Other	44 (9.6%)	3 (7.5%)
Total	460 (100%)	40 (100%)

*Guillain-Barré Syndrome
Source: Izurieta, Haber. *JAMA*. 2005.

Adverse Events after FluMist® in 15 Children Aged <5 Years: Main Condition Reported to VAERS 8/1/2003–2/28/2007

Adverse Event	N
Vaccine administration error	6
Secondary transmission	2
Rash/ other allergic	2
Rhinitis	2
Abdominal	1
Seizure	1
Vaccine failure	1

Source: Hua W., Haber P, Izurieta H, unpublished VAERS data